MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS OF THE CORONARY CIRCULATION

Harvey Lecture, April 18, 1940

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PROBLEMS for investigation which have their origin in the clinic frequently lead the investigator far afield in the course of his search for suitable methods for their solution. Interesting side trips into pathology, physiology or chemistry may result when he is forced to use the methods or seek the help of his colleagues in these subjects. And so it is with the work concerning which I have the honor to speak to you this evening. It had its origin in the clinic and has been carried on during the past ten years in the Department of Medicine of the Lakeside Hospital and Western Reserve University. In the various stages of the work I have had the privilege of having with me a number of younger collaborators, and we have sought and obtained aid frequently from our colleagues, particularly in physiology, chemistry, and pathology. The final result, therefore, may be said to be the product of all of these.

The coronary vascular tree, which supplies blood to the heart, is—with its various ramifications and anastomoses—one of the most complex vascular systems in the body. For this reason, it seems wise to begin with a description of the structure of the coronary circuit and its numerous component parts.

When Galen[1] first applied the name "coronary" to the larger arteries of the heart he was in doubt, apparently, as to whether there was one or two such vessels, and the confused conception which he held concerning their function is brought out by his suggestion that the arteries ended as nerves. It was not until the great publication of William Harvey[2] that the first clear statement of their function appeared. In his *De Motu Cordis*, Harvey states that the heart has a supply of blood for its own especial behoof, in its coronary veins and arteries—". . . hic locus autem cor est; cum solum ex omnibus partibus (non solum in vena &

arteria coronali privato usui) sed in cavitatibus suis tanquam in cisternis, & promptuario (auriculis scilicet & ventriculus) publico usui, sanguinem continet: . . ."

The coronary vessels are shown in the anatomical drawings of Leonardo da Vinci, but it was not until the work of Richard Lower[3] in 1671 that more accurate data concerning the arteries and veins of the heart began to appear. Lower was the first to describe anastomoses of the branches of the arteries, which he demonstrated by showing that liquid which he injected into one artery escaped from the other. Friederic Ruysch[4] in 1704 introduced the corrosion method of studying blood vessels and showed the distribution of their branches. Almost simultaneously Raymond Vieussens,[5] in 1706 and 1715, published the results of his brilliant studies on the heart. His beautiful dissections of single branches of the coronary arteries revealed the distribution of the vessels in the various muscle layers. Of greater significance, however, was his discovery of a new group of blood channels in the heart wall. While opening human hearts at necropsy, he observed that the blood clots, so frequently seen in the heart chambers, had attached to them little tendrils which ran into small openings in the heart walls. Being convinced that these openings were connected with the coronary circuit, he injected saffron into the coronary arteries and observed its escape through the small openings into the auricles and ventricles. Two years later, in 1708, Adam Christian Thebesius[6] demonstrated a connection between the coronary veins and the openings in the heart walls. His experiment —simple and convincing—consisted of blowing air into the coronary veins, with the heart immersed in water, and observing the bubbles of air escape through the openings in the heart wall. Since then these vessels have been known as Thebesian veins, but, as will be shown presently, Vieussens and Thebesius, though unaware of it, were dealing with different groups of vessels which were separated by the capillaries.

In 1798, Abernethy[7] confirmed the results of Vieussens, and, while he did not fully appreciate the significance of his findings, his experiments demonstrated vascular communications between the chambers of the heart and the arterial side of the coronary circuit.

These interesting discoveries were lost sight of, and until the past score of years they have been ignored in almost all anatomical and physiological studies of the coronary system. Recently Kretz[8] and more particularly Crainicianu[9] began to recognize their importance. The latter

showed for the first time that the aggregate diameter of the luminal vessels was almost equal to that of the coronary arteries.

In 1928,[10] when we perfused the coronary arteries and collected the outflow from the coronary sinus and the chambers of the heart, we were astonished to find that approximately 80 per cent of the fluid escaped from the luminal vessels and only 20 per cent from the coronary sinus. It was natural, then, to ask ourselves what role these vessels might play in the circulation of the heart and what relationship they might bear to the arteries, capillaries, and veins. In work with S. R. Mettier in 1928 it was found that if a solution of celloidin too thick to penetrate capillaries was introduced into the coronary arteries some of it escaped by way of the luminal vessels into the chambers of the heart. In another experiment the ventricular chambers were filled with a solution of red celloidin. Suction applied at the ostia of the coronary arteries drew the celloidin into the openings of the luminal vessels. Blue celloidin was then injected into the coronary arteries where it fused with the red. When the muscle was digested off, casts of the arterial luminal vessels were revealed.

These vessels were also demonstrated by wax reconstruction. One of the openings of the luminal vessels in the ventricular wall from which the celloidin protruded was selected under the dissecting microscope and marked with India ink. The muscle containing this vessel was then cut into serial histological sections. Study and wax reconstruction of these sections, in collaboration with T. G. Klumpp and L. J. Zschiesche,[11] revealed two types of vessels which connected the arterial side of the coronary circuit with the heart chambers; one direct from the arterioles, and the other through the myocardial sinusoids directly into the chambers. The more direct arterio-luminal vessels are not numerous, but the arterio-sinusoidal vessels occur in large numbers and are easily recognized. Their structure, except for the irregularity of the lumen, is identical with that of the capillaries. It is quite possible, therefore, that the metabolic exchange through their walls is the same as that which occurs through the capillary walls.

The Thebesian veins are connecting channels between the capillaries and coronary veins on the one hand and the heart chambers on the other. This was shown in our laboratory in 1928, and the excellent work of Grant[12] has demonstrated the various branchings and communications of these veins.

Of the remaining larger branches of the coronary arteries the extracardiac vessels are worthy of note. First described by Albrecht von Haller in 1803,[13] these vessels leave the heart around the root of the aorta and around the ostia of the superior and inferior venae cavae, and in the intervascular pericardial reflections. In work with C. L. Hudson and A. R. Moritz, 1932,[14] they were shown to anastomose with the arteries supplying the aortic wall, the pericardium, the upper and lower surfaces of the diaphragm, the pleural surfaces of the lungs, the trachea and esophagus.

The capillaries of the myocardium are very difficult to recognize; indeed, in the ordinary histological section only an occasional capillary can be identified. In order to visualize the capillary bed, injection of dyes through the coronary arteries or veins must be resorted to. In the dead heart, however, the luminal vessels offer less resistance to the injection mass than do the capillaries; consequently, in most instances attemps to inject the capillaries via the coronary arteries fail, and the mass escapes into the heart cavities through the luminal vessels. Attempts to fill the capillaries through the coronary veins likewise fail because the mass escapes through the Thebesian veins. We found, in 1928,[10] that if a heart can be revived by perfusing it with an oxygenated Locke-Rosenheim solution, the capillaries can be injected without difficulty by adding dye to the perfusate.

With the capillary bed visible it was an easy matter to trace its connections not only with the arterioles and venules, but with the sinusoids and Thebesian veins as well. As a result of these observations it is now possible to construct a diagram of the coronary circulation.

The coronary arteries, as shown in Figure 1, may communicate with extracardiac arteries, with ventricles through the arterio-luminal and arterio-sinusoidal vessels, and finally with one another. If there be any doubt of the existence of communications between the different trunks of these arteries, the preparations of Spalteholz[15] and Gross[16] should dispel it, for in the anatomical sense, at least, these workers have shown that the coronaries are not end arteries. Moreover, even in the event of complete closure of the ostia of the coronary arteries the heart still has access to a blood supply at arterial pressure levels through the extracardiac and arterio-luminal vessels. Two cases reported with Timothy Leary,[17] in 1930, show that the heart is capable of sustaining an active life with the mouths of both coronary arteries occluded. Since reporting

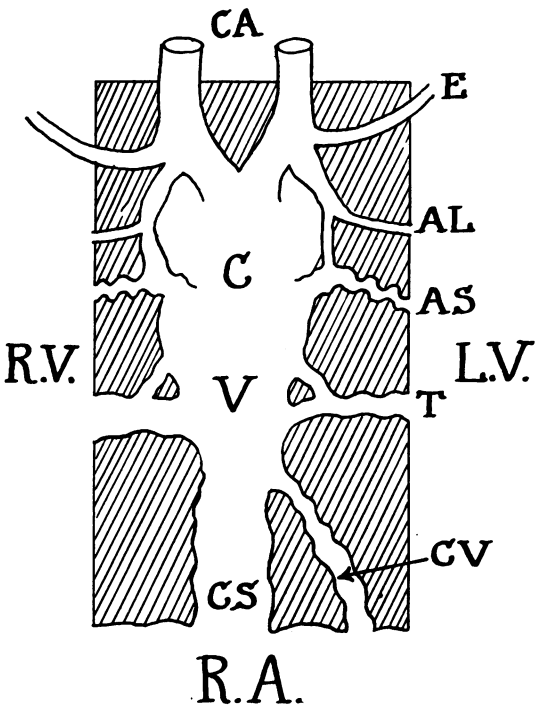

Fig. 1

CA—coronary arteries.
E—extracardiac branches.
AL—arterio-luminal vessels.
AS—arterio-sinusoidal vessels.
C—capillaries.
T—Thebesian veins.
V—coronary veins.
CV— " "
CS—coronary sinus.
R.V.—right ventricle.
R.A.—right auricle.
L.V.—left ventricle.

these cases, a number of others with occlusions of one or both coronary arteries have been recorded. Despite the occlusion of whole arteries, infarction of these hearts did not occur.

The question naturally arises as to how these hearts get their blood supply. In the event of occlusion of the ostia of both coronary arteries one can only conclude that the arterial blood must come either from the extracardiac vessels or from the arterio-luminal vessels. But I know of no evidence that would indicate whether one or both of these sources are utilized. No other channels of sufficient size to supply enough blood to maintain normal heart action are known to exist.

In the event of the closure of the ostium or of a large branch of one

coronary artery, Schlesinger[18] has shown that, if given sufficient time, anastomoses will develop from other branches of the artery. The work of Mautz and Beck[19] on dog hearts would indicate that in these animals closure of one coronary artery results in marked enlargement of the already existing anastomoses. In their experiments a large branch of one artery was tied off in gradual stages. This gave sufficient time for the collateral anastomoses to develop. Supportive evidence is also found at autopsy, in instances where syphilitic aortitis or advanced coronary sclerosis may completely occlude one or both major branches of the coronary arteries without the production of infarction. One important factor should be pointed out at this time, and that is the factor of time. All of these processes require weeks, if not months or years, to bring about the gradual closure of the main trunks of the arteries, thus giving ample time for the existing anastomotic channels to begin to function.

The role that the luminal and Thebesian vessels play in the circulation of the normal heart has received very little attention. Evans and Starling,[20] Markwalder and Starling,[21] Anrep and Hausler, 1928,[22] and others have shown that part of the blood entering the coronary arteries does not return through the coronary sinus, and they have assumed, with Thebesius, that the luminal vessels serve only as auxiliary veins. These workers, unfortunately, did not observe pressures within the chambers of the heart, nor did their studies take into consideration the possibility of an ebb and flow of blood in the luminal vessels. The flow from the luminal vessels, under the conditions of their experiments, was constant at about 40 per cent of the coronary artery inflow.

Stella[23] found no flow from the peripheral ends when he cut the coronary arteries. His animals lived for two minutes at most after the arteries were cut, and the hearts failed instantly, so allowance must be made for the fact that these experiments were made on moribund animals.

Bohning, Jochim and Katz[24] injected killed cultures of staphylococci and hay bacilli and other particulate matter into the vena cava, under conditions which precluded entrance of the injected material into the coronary arteries. They found the bacilli in the capillaries of the heart wall, and concluded that the luminal vessels act as a source of blood supply in normal hearts.

Recently, Wiggers[25] has approached the question of the direction of flow of blood in the luminal and extracardiac vessels from a theoreti-

cal standpoint, taking into account the pressure relations and the pressure gradients available for flow through anastomotic channels, if they exist.

Under normal conditions, the pressure gradients are such that a transfer of blood from the coronary arteries to the left ventricle could occur during the whole of diastole and during the early part of isometric contraction. In the right ventricle and auricles, on the other hand, the pressure gradients are such that a theoretical transfer of blood could occur throughout systole and diastole.

The practically identical pressures in the coronary arteries and extracardiac anastomoses would prevent any flow of blood between them at any time in the cardiac cycle.

If one examines the pressure relations that exist when the coronary ostia are occluded, as shown in the curves of Wiggers,[26] it is obvious that the pressure gradients are ideal for flow from the ventricle into the luminal vessels and sinusoids, but the answer to this question must await experiments not yet complete.

During the past two years, with Doctors D. E. Gregg, R. W. Eckstein, and J. T. Roberts, work* has been carried on in our laboratory with the purpose of finding out the direction of the flow in the luminal vessels in the right ventricle and the effect upon the flow of changing pressures within that chamber. By means of a shunting device with a two-way valve introduced into the pulmonary artery of a dog it was possible to allow the blood entering the pulmonary artery to flow through the device directly into the pulmonary arteries, as usual, or, by turning a cock, to shunt the blood from the right ventricle into a rubber balloon which, as it filled, displaced an equal volume of blood from the flask outside the balloon back into the pulmonary artery. In this manner Chicago blue or India ink was introduced into the right ventricle without the possibility of its reaching the lungs or the coronary arteries. During the experiment right and left ventricular pressures were recorded.

After introduction of the shunting device the pressures were allowed to become constant, with the blood flowing directly through the pulmonary artery. The usual pressures were about 100/7 in the left ventricle, and 19/2 in the right ventricle. Blood was then shunted into the balloon and India ink was introduced into the vena cava at such rate that

* This work, and the metabolic studies reported later in this paper, were made possible by a grant from the Commonwealth Fund.

the right ventricular pressure was not changed. At the desired time the heart was stopped by the introduction of KCl or glacial acetic acid into the left ventricle. It was then fixed, sectioned, and examined microscopically for the presence of India ink in the vessels of the myocardium.

These experiments gave convincing evidence that the pressure gradient between the right and left ventricles determined the direction of flow in the luminal vessels of the right ventricle. So long as the pressure in the left ventricle was greater than that in the right, no significant flow took place from the ventricle into the luminal vessels. There was an occasional superficial vessel in the septum that contained ink, but these extended less than 2 mm. below the endocardial surface. The capillary bed, by gross and microscopic examination, was free from injection mass.

If, at the time of injection of the ink, the right ventricular pressure was greater than the left, a very significant flow took place from the ventricle into the luminal vessels, as evidenced by a complete injection of the capillaries and larger vessels. When the capillaries were filled with ink the heart was grossly black, and this observation was utilized in a third experiment. In the beginning, with the left ventricular pressure definitely higher than the right, an injection of ink into the vena cava was begun. The heart remained red in gross appearance—evidence that the ink was not entering the myocardial vessels from the ventricle. The pressure relations were then changed by raising the right ventricular pressure and lowering that in the left ventricle simultaneously. As the pressures became equal the ink began to enter the luminal vessels and the heart turned black the instant that the right ventricular pressure exceeded that of the left. Inasmuch as these observations were made in the intact animal, the conclusion is drawn that there is no flow of blood from the right ventricle into the luminal vessels, under normal conditions.

Support is given to these results by the following experiments in rabbits. If Chicago blue is injected into the right ventricle of a normally beating heart at a pressure insufficient to raise the right ventricular pressure to that of the left ventricle the heart turns blue only after the dye has passed through the lungs and entered the myocardial capillaries via the coronary arteries. If, after injection of the dye into the right ventricle, the heart is allowed to beat two or three times and at this point the right ventricular wall is suddenly opened with a pair of scissors near the pulmonary artery, the right ventricular pressure drops to zero and

the dye never reaches the left ventricle. Microscopic examination reveals no dye in the myocardial vessels.

The normal function of the luminal vessels in the left ventricle is unknown.

Capillary Bed

The normal relationship of the capillaries to the muscle fibres which they supply with blood is of considerable importance. They communicate freely, not only with arterioles and venules, but equally with all the luminal connections. Thus, the muscle fibres enjoy several possible sources of blood supply. It has long been known that at the time of birth the muscle fibres are small in diameter. During physiological growth the fibres increase in diameter and length, thus increasing the thickness of the heart wall, the capacity of its chambers, and the total heart weight. There are also concomitant changes in the blood vessels of the heart. Ehrich, de la Chapelle and Cohn,[27] for instance, found that the arteries of each ventricle increase in direct proportion to the weight of the ventricles.

The muscle fibres, the capillary bed and the quantitative relationship between the two were studied in our laboratory during growth, in rabbits and in man, in 1937, in collaboration with R. A. and L. J. Shipley,[28] and during the past three years in human hearts, with J. T. Roberts.

Certain precautions are necessary in studying quantitative changes in muscle fibres and capillaries. First, a method of fixation and mounting the histological sections must be used which will avoid the errors that result from shrinkage. Secondly, accurate determination of the number of capillaries depends upon complete injection of the capillary bed in the section of tissue studied. In our hands, this has been uniformly successful only in those hearts which were revived and injected while beating. In only a few instances have successful injections been made by other methods in hearts obtained more than six hours postmortem.

At the time of birth, in the rabbit heart, there was one capillary for every five or six muscle fibres. The capillaries were evenly distributed and ran parallel to and alongside the fibres. In the human heart the same relationship was observed. In the heart of a seven months' fetus there was one capillary to six muscle fibres, while in the heart of an infant three weeks old, the ratio was four fibres to each capillary.

With the increase in diameter of the muscle fibres as a result of

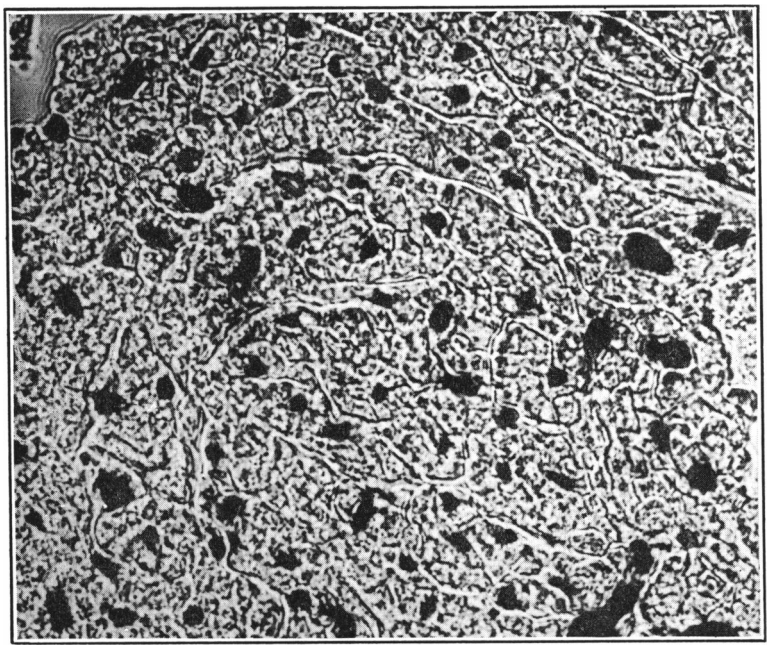

Fig. 2—Heart of infant (3 wks.). Note small fibres.

growth, the fibre-capillary relationship began to change, so that in the heart of a child sixteen years of age there was one capillary for two muscle fibres. This change in the ratio of fibres to capillaries continued until growth was completed, at which time the ratio of fibres to capillaries was approximately 1:1. We have relatively few observations on the hearts of growing rabbits and of children, with no children's hearts between the ages of one and eight years, but, as will be seen in Figures 4 and 5, the curve of the fibre-capillary ratio in the human heart is almost identical with that in the rabbit heart. Moreover, this curve seems to take the form of a hyperbole, which is a form frequently observed in growth phenomena.

Once growth is completed, the fibre-capillary ratio remains constant, at approximately 1:1, so long as the heart remains normal, both in man and in the rabbit.

In a group of twenty-six normal hearts of adults the fibre-capillary ratio ranged from 0.97 to 1.68, with an average of 1.34 ($\pm$0.023). The remarkable uniformity of this figure throughout the group is in sharp

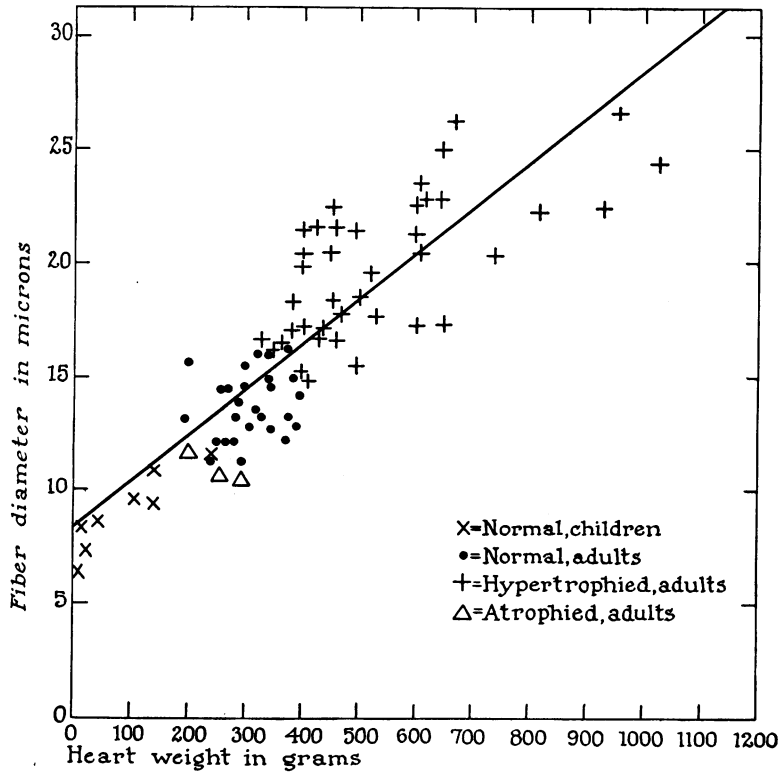

Fig. 3—The influence of growth, hypertrophy and atrophy on fibre diameter.

contrast to the constantly changing one during growth.

It has been claimed by Tangl[29] that the increase in fibre diameter during growth may be as much as six-fold. Our observations show an increase in human hearts during growth of five-fold. Findings in the rabbits were of the same order. Thus, the one capillary which at birth supplied five muscle fibres, in the adult supplies one fibre, the area of which is approximately that of five fibres at birth.

In view of the increasing mass of muscle and the changes in the fibre-capillary ratio during growth, it is interesting to observe the effect of this change upon the concentration of capillaries in a square millimeter of heart muscle. In the human heart at birth there were approximately 4000 capillaries per square millimeter. This concentration remained essentially the same in children's hearts throughout the period of growth, the average for all children's hearts being 3700. The same constancy was

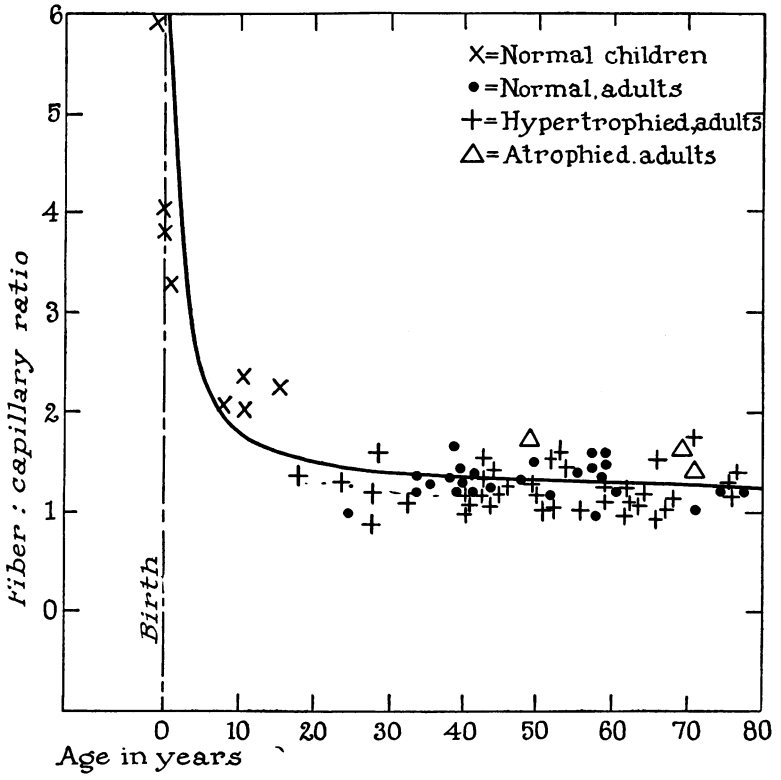

Fig. 4—The influence of growth, hypertrophy and atrophy on the number of fibres per capillary.

found in the concentration of capillaries in the rabbit hearts.

The changes occurring during growth of the heart may be summarized as follows: At birth there are five muscle fibres to each capillary. As the fibres increase in size the fibre-capillary ratio changes constantly until there is approximately one capillary for each muscle fibre. Throughout the growth period the concentration of capillaries per unit of area is maintained at a constant level. It is obvious, therefore, that the increase in muscle mass is accompanied by a corresponding increase in the total number of capillaries.

In the normal hearts of adults the capillary concentration also remains remarkably constant. In the twenty-six hearts with an age range from twenty-five to seventy-seven years, the number of capillaries per square millimeter ranged from 3000 to 4000, with a mean of 3342 ($\pm$36). The standard deviation for the entire group was only eight

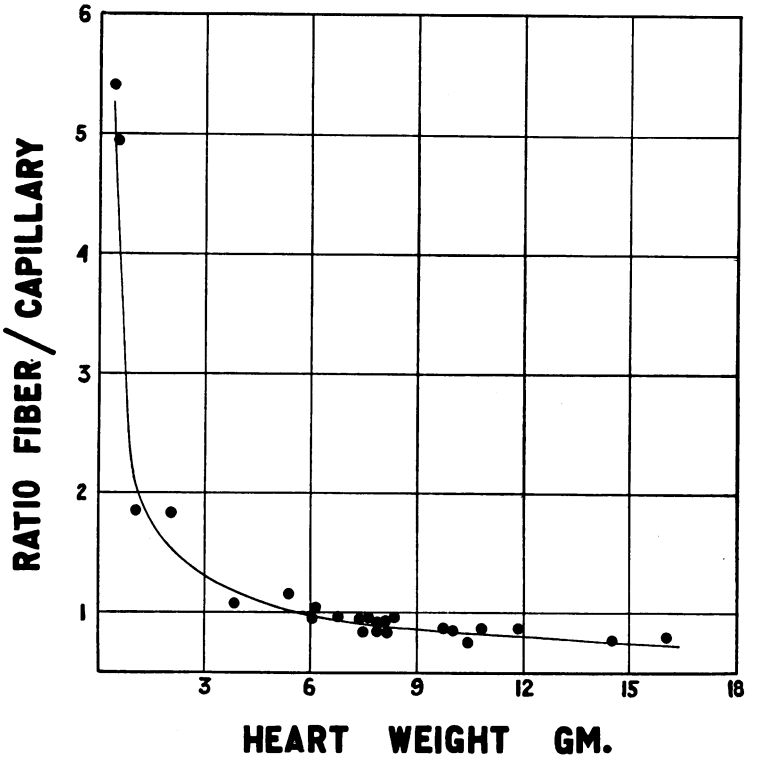

Fig. 5—The influence of growth upon the fibre-capillary ratio in rabbits (after Shipley, Shipley and Wearn). Reproduced by courtesy of the *Journal of Experimental Medicine.*

per cent and, when one considers the wide age distribution for the group, the capillary concentration is obviously fairly constant throughout adult life, so long as the heart remains normal.

The muscle fibres in the hearts of normal adults also remain fairly uniform in size, with a mean diameter for the group of fourteen micra.

We then undertook to find out if any changes occur in the muscle-capillary relationship during cardiac hypertrophy. Indeed, it was this question which prompted this work in 1923. It became necessary to establish the normal relationships described above before we could proceed with the problem of hypertrophy.

The frequent finding at necropsy of an hypertrophied heart that has failed is familiar to all. Other than the hypertrophy, the muscle of these hearts often shows no abnormalities. Why, then, should an enlarged muscle without demonstrable abnormality fail? Hypertrophy is fre-

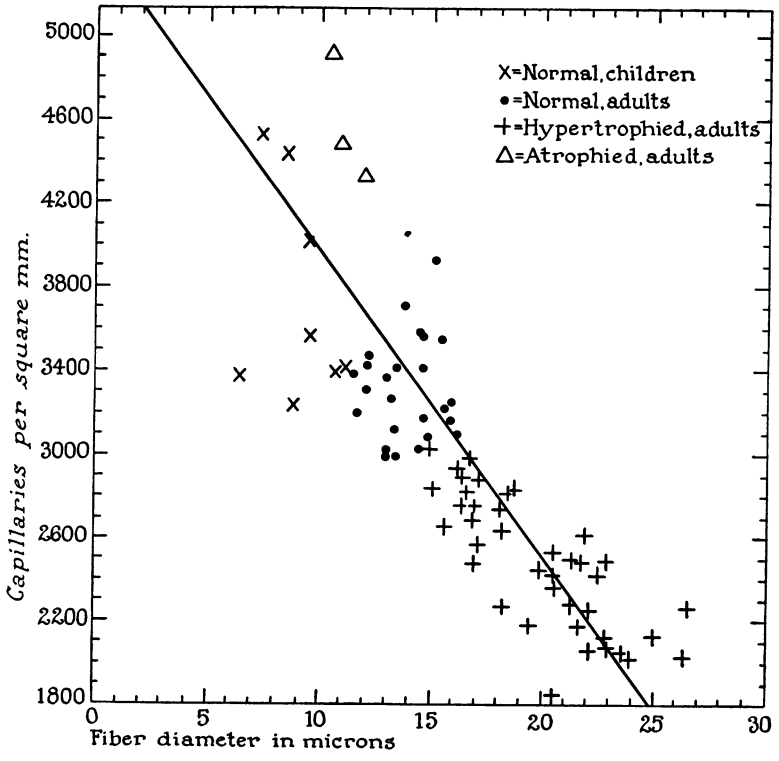

Fig. 6—The influence of fiber diameter on the capillary concentration.

quently spoken of as being compensatory. On the other hand, it is also considered to be one of the most dependable signs of heart damage. There is no factual evidence, so far as I can learn, to support the claim that an enlarged heart is a more efficient performer. It occurred to us that the enlargement of the heart might result in a diminution of blood vessels in the heart wall. The exact problem may be stated in this way: Is it possible that during the enlargement of the muscle, the capillaries do not increase proportionately? If this should prove to be true, hypertrophy would result in an actual decrease in the concentration of capillaries per unit of tissue.

In order to answer this question, observations similar to those carried out on growing hearts were made on a group of hypertrophied hearts. There was clinical and pathological evidence of disease in all of these hearts. Hypertension, rheumatic fever, syphilis, and coronary sclerosis were frequently present. Death was the result of congestive failure in

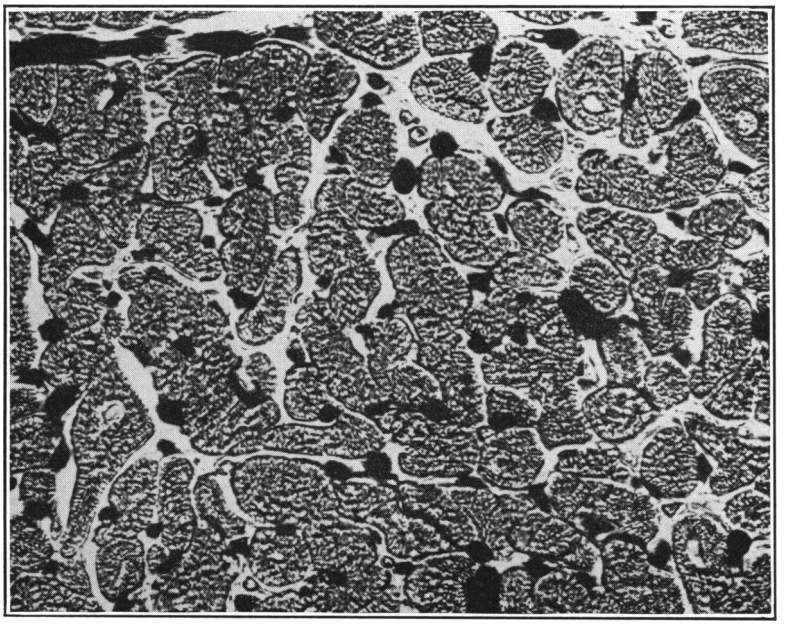

Fig. 7—H 30. Wt. 300 gm. Capillaries 3551 per sq. mm. Fiber diam. 15.5 micra.

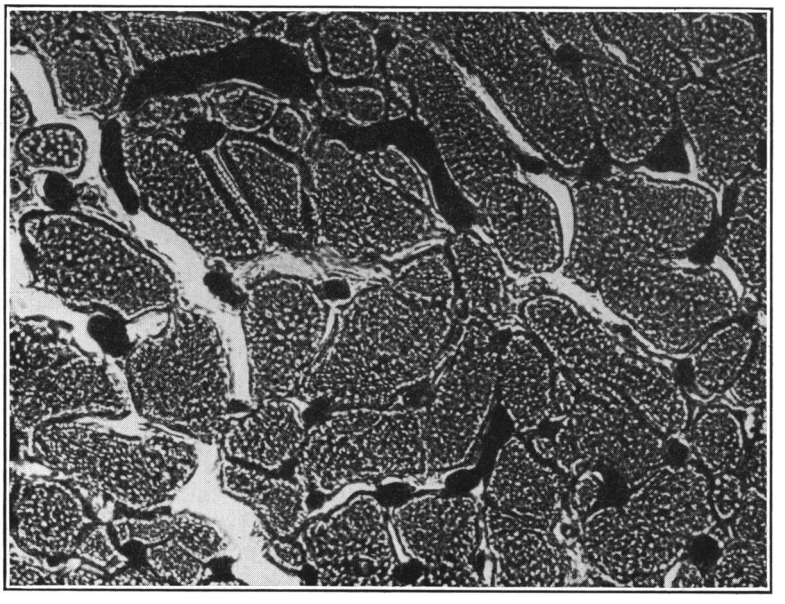

Fig. 8—H 52. Wt. 930 gm. Capillaries 2251 per sq. mm. Fiber diam. 22.1 micra.

the majority of these patients.

The degree of hypertrophy varied considerably. Some of the hearts showed so little enlargement that they might well have fallen within the normal group. At the other extreme was a heart weighing 1150 gm. The average weight for the group was approximately 525 gm. (±16.1).

During hypertrophy the muscle fibres increased in size throughout the heart. The enlargement was in almost direct proportion to the increase in weight of the heart. In many instances some of the fibres reached diameters triple those of normal heart fibres.

Despite the marked increase in size of the fibres, the fibre-capillary ratio showed practically no change. The ratio of approximately 1:1 was as uniform in this group as in the normal hearts.

The most striking change found during hypertrophy was observed in the concentration of capillaries in the muscle. As the muscle fibers increased in diameter the capillaries were pushed farther apart, and this resulted in a decrease in the concentration of the capillaries per unit area of muscle. The concentration of the capillaries diminished in proportion to the increase in the fibre diameter and to the increase in heart weight. Thus, the larger the heart, the less the concentration of capillaries.

With these data concerning growth and hypertrophy in hand it becomes clear that they are separate and distinct processes. Growth of heart muscle is accompanied by a proportional increase in the number of capillaries, while hypertrophy of the muscle results in an actual decrease in concentration of capillaries. It would avoid a great deal of confusion if we reserve the term "hypertrophy," as applied to hearts, to those that show changes in keeping with this definition. The much discussed increase in size of the hearts of young athletes is frequently spoken of as hypertrophy. But whether it is actually hypertrophy or growth can be settled when such hearts are subjected to the type of study just described.

Atrophied Hearts

Three hearts, atrophied as a result of wasting disease, were studied. The muscle fibre diameter decreased and the capillaries moved more closely together, resulting in an increase in the capillary concentration.

In all quantitative measurements of muscle and capillary-muscle relationship which have been described up to this point our observations

TABLE I

	AV. HEART WT.	MEAN AGE	AV. HT. WT. BODY WT. RATIO	AV. FIBRE DIAM.	AV. NUMBER CAPILL. PER SQ. MM.	AV. FIB./CAP. RATIO
	gm.			*mu*		
Child*	20	3 wk.	0.0069	7.4	4513	4.04
Normal adult.....	310	51	0.0054	13.9	3342	1.34
Hypertrophy.....	535	49	0.0088	19.8	2483	1.23
Atrophy	247	66	0.0043	11.1	4613	1.69

* Single heart for comparison.

were confined to muscle bundles of myocardium in order to obtain an accurate picture of the functioning muscle. Recently, we have studied some of these hearts in a different manner. The same measurements were made, but instead of confining the observations to muscle bundles, cross sections of the whole heart tissue were studied so as to include scars, large fibrous septa lying between muscle bundles, etc. A comparison of these results with those obtained from the study of the muscle revealed in some instances some interesting results.

In the hypertrophied hearts the inclusion of counts on the whole tissue caused a marked drop in the total capillary concentration, sometimes to less than half that in the muscle bundles.

Microscopical studies of the scarred areas in the hypertrophied hearts showed a marked disturbance of the muscle-capillary relationship. Muscle fibres were frequently partially or completely surrounded by scar tissue, and fibres in various stages of degeneration were found. The important point, from our viewpoint, was the fact that many of these fibres were without capillaries. In many fields, also, the capillaries were fairly evenly distributed in the scar tissue where the fibres had completely disappeared.

It is obvious that the efficiency of fibres without capillaries and of capillaries without fibres in performing their respective functions might be seriously interfered with.

With the guidance and help of Professor J. R. Musselman of the Department of Mathematics of Western Reserve University we have studied the data of the quantitative relationship of the capillaries to the muscle mass. It was found that a high order of correlation exists—so

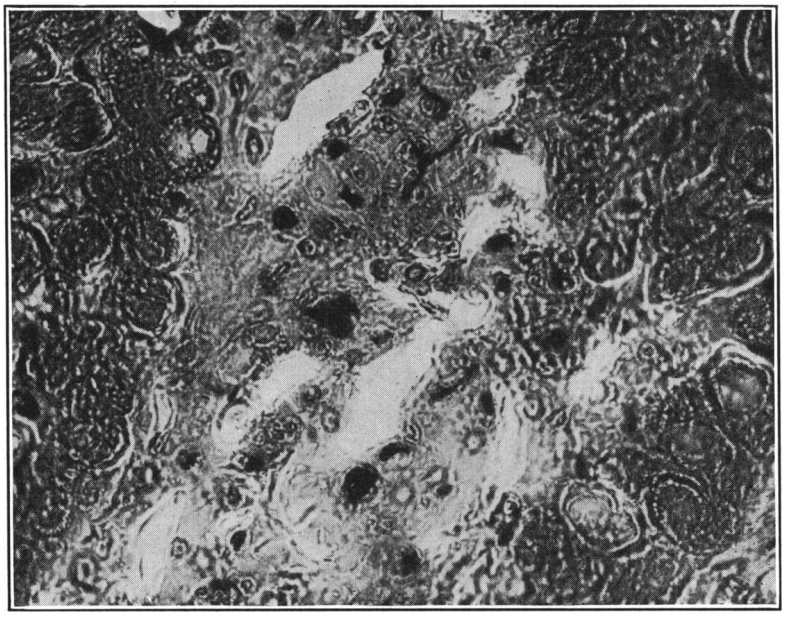

Fig. 9—Scar in myocardium (rheumatic fever) showing distribution of capillaries.

high at times that it suggests the possibility of a governing biological law. There is, for instance, a practically perfect positive correlation between the heart weight and the average muscle-fibre diameter. Thus, if the heart weight is known, the average muscle-fibre diameter can be calculated with a probable error for the predicted value of ± 1.435 mu.

Likewise, between the average fibre diameter and the number of capillaries per sq. mm. there is a close correlation and, if the fibre diameter is known, the capillary concentration can be calculated with a probable error for the predicted value of ± 209 capillaries.

As a result of these two correlations, the expected correlation between the heart weight and the capillary concentration was found to exist, so that, given the heart weight, the capillary concentration can be calculated.

And, in similar manner, the fibre-capillary ratio can be predicted from the patient's age.

One can also calculate the capillary surface area available for the diffusion of oxygen and the exchange of metabolites in a cubic centimeter of muscle. This was found to be:

Hearts of children	1145	sq. cm.
Adults (normal)	1184	" "
Hypertrophied	623	" "

When this ratio is plotted against the heart weights (Chart V), the hearts of children and normal adults show the same wide range, without apparent correlation to heart weight. The hypertrophied hearts fall well below the range of the normal hearts and show a definite rectilinear negative correlation of high degree with the heart weight. This we interpret as showing that, in the normal hearts of children or adults, the capillary surface per cubic centimeter of muscle is constant and independent of heart weight.

At this point the temptation to speculate is almost irresistible. Our observations on the changes during hypertrophy show that, as the heart enlarges, the distance from the capillary wall to the periphery of the muscle mass which it supplies becomes greater. This means that the route over which oxygen has to diffuse and metabolic products have to travel increases in proportion to the degree of hypertrophy. Moreover, the actual capillary surface available for exchange is markedly decreased per cubic centimeter of muscle. It seems safe to say that at some stage in the course of hypertrophy a point will be reached where metabolic exchange will be seriously interfered with.

Chemical studies designed to find out whether hypertrophy interferes with the exchange of metabolites are not yet sufficiently advanced to answer this question, but a few observations have been completed and are perhaps deserving of brief mention.

The oxygen utilization by the heart muscle has, in the past, been studied, for the most part, either in isolated hearts or heart-lung preparations. Katz and Long[30] have shown that skeletal muscle can establish an appreciable oxygen debt without harm, whereas heart muscle in the same animal can tolerate very little oxygen debt. Indeed, any appreciable diminution in the oxygen in the arterial blood reflects itself immediately in the weakening of the heart beat.

Oxygen, of course, is required for the removal of lactic acid, and it was shown by these workers, as well as by others, that the heart tolerates only about one-quarter of the lactic acid concentration that skeletal muscle does. The heart, therefore, is dependent upon its contemporary oxygen supply in order to function efficiently.

Hastings and Blumgart[31] have recently found that brief periods of

TABLE II

Coronary arterial-venous oxygen difference in dogs

OXYGEN CAPACITY	OXYGEN CONTENT					
	Arterial		Coronary vein		Femoral vein	
vols. %	*vols. %*	*% sat.*	*vols. %*	*% sat.*	*vols. %*	*% sat.*
15.1	12.7	84	2.6	18	12.3	82
17.6	16.1	92	3.1	18	12.8	73
18.1	17.6	97	9.8	53	13.3	74
20.7	20.2	98	5.0	24	15.3	74
19.8	18.8	95	6.2	31	13.1	66
15.5	12.5	81	3.6	23	7.8	50
23.1	21.0	90	3.7	16	15.7	67
21.8	19.1	88	2.8	12		
21.2	18.1	85	2.6	12		
22.1	17.2	79	3.3	15		
23.5	20.5	88	3.7	16		

anoxemia produce measurable chemical changes in heart muscle, in the absence of histological change.

In work now in progress with J. W. Price and D. E. Gregg, the oxygen utilization of the normal heart is being determined in the dog. With the animal anesthetized and, therefore, at complete rest, blood samples have been collected under proper conditions and as nearly simultaneously as possible, from the left ventricle, the coronary sinus, and in some instances from the femoral vein.

The percentage saturation of oxygen in the venous blood from the coronary sinus was constantly and surprisingly low. The figures ranged from 12 per cent to 53 per cent, with an average of 23 per cent, whereas the average saturation of the femoral venous blood was 70 per cent.

The following experiment illustrates the methods used. The heart was exposed under sodium pentobarbital anesthesia with artificial respiration. In some instances the chest was closed and made air tight by means of the pericardium, which was sewed to the walls to form a cradle in which the heart could beat outside the chest. This procedure also enabled the animal to breathe normally. Care was exercised to avoid tension on the vessels and nerves at the base of the heart. Each set of three blood samples was taken within a period of five minutes. The following results from one experiment are typical:

DATE	CORONARY VEIN			RIGHT VENTRICLE			LEFT VENTRICLE		
	O_2 content	O_2 capacity	Saturation	O_2 content	O_2 capacity	Saturation	O_2 content	O_2 capacity	Saturation
	vols. %	*vols. %*	%	*vols. %*	*vols. %*	%	*vols. %*	*vols. %*	%
2/15/40	4.6	21.8	21	14.8	21.7	68	21.3	21.8	98

TABLE III

Percentage O_2 saturation

	ARTERIAL	VENOUS	
Himwich & Castle.....	92–108 av. 99	12–64 av. 38	Gastrocnemius, exercised
Barcroft & Kato.....		51–70	"
Price, Gregg & Wearn....	79–97	12–53 av. 23	Heart anesthetized dog

Oxygen capacity was determined on each blood sample and each percentage saturation value was calculated from corresponding content and capacity values.

Barcroft and Kato, in 1915,[32] and Himwich and Castle,[33] in 1927, determined the O_2 utilization in the resting and exercised leg muscles of dogs. A comparison of their findings with ours is shown in Table III.

From these figures it is obvious that percentage saturation of the venous blood of the heart of a dog at rest is significantly lower than the venous blood from exercised skeletal muscles. The heart, in what might be called a resting state, therefore, leaves very little oxygen in the coronary venous blood.

This almost complete use of available oxygen by the normal heart offers a plausible explanation for the findings of Katz and Long that the heart will not tolerate an oxygen debt. It also suggests that any increase in work by the heart must be met by an increase in the coronary blood flow, which could be brought about either by the opening of additional capillaries or by an increase in the velocity of the flow of blood in those capillaries already open.

In regard to the opening of additional capillaries it may be said that in numerous experiments in our laboratory we have never been able to demonstrate an intermittence of flow in the capillary bed of the myocardium, nor has any convincing evidence of intermittence ever been published, of which I am aware. Our work is still in progress, but it seems very likely that the heart uses all of its capillaries at all times. The mechanism available, therefore, for meeting strain is most probably an increase in blood flow in the coronary circuit.

It is now generally accepted that the muscle pigment also plays a role in oxygen transfer and storage. Whipple[34] and his co-workers[35] have shown that myoglobin, or muscle hemoglobin, is present in the myocardium of puppies to the extent of 100–200 mg. per 100 gm. of muscle, increases to 300 mg. at puberty, and reaches 300–400 mg. in adult dogs. They showed that exercise or activity can increase the amount of pigment in the myocardium and the lowest values were encountered in the most inactive animals.

Hurtado et al.[36] observed that dogs kept at high altitudes in the Andes have more myoglobin than dogs kept at sea level. This finding was interpreted as an adaptation to facilitate O_2 exchange in the face of chronic anoxemia.

In view of the increase of myoglobin in heart muscle during normal growth and during the chronic anoxia of high altitudes, we have begun observations upon the muscle hemoglobin in normal and hypertrophied human and rabbit hearts. While our data are too few to justify final conclusions, we have found, thus far, no appreciable difference in the myoglobin content of normal and hypertrophied hearts of rabbits or man. These results are in keeping with those of Cowan and Bauguess,[37] who found no increase in myoglobin in hypertrophied hearts in rats. If these findings prove to be constant they will represent another fundamental difference between the process of hypertrophy and that of normal growth.

Several changes occur in hypertrophy, therefore, which at some stage of the enlargement will impede oxygen diffusion and the exchange of metabolites. At what point during the process of hypertrophy and to what extent they interfere must await further study of the metabolites with a simultaneous measurement of the flow of blood in the coronary arteries.

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